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Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ,*

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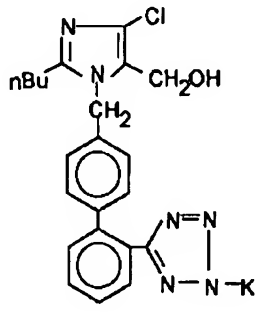
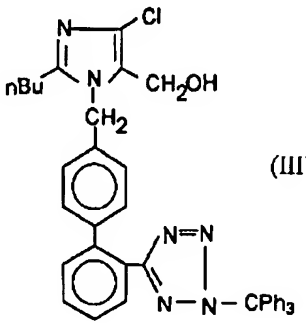
(54) Title: PROCESS FOR THE SYNTHESIS OF A KNOWN TETRAZOL DERIVATIVE



(I)



(III)

R—OH (VI)

(57) Abstract: The invention relates to a process for the synthesis of losartan potassium of formula (I), chemical name: 2-n-butyl-4-chloro-1-[(2'-(tetrazol-5-yl)-1,1'biphenyl-4-yl)-methyl]-imidazol-5-methanol potassium, starting from 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmetyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol of formula (III). According to the process the compound of formula (III) is reacted in an alcohol of formula (VI), - wherein the meaning of R is C_1-C_4 straight chain alkyl group -with 0.1-1 equivalent of potassium hydroxide. The final product of formula (I) is isolated after crystallizing out by changing the solvent to an aprotic or weakly protic solvent (I).

WO 01/81336 A1

UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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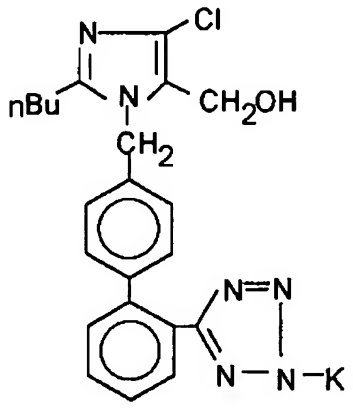
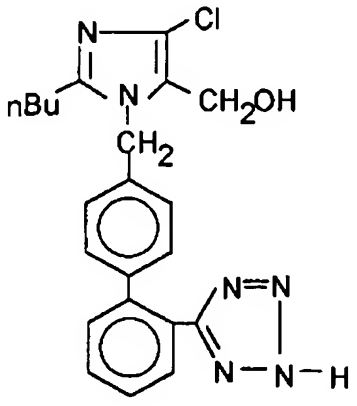
Process for the synthesis of a known tetrazol derivative

The invention relates to a process for the synthesis of a known tetrazol derivative of formula (I).

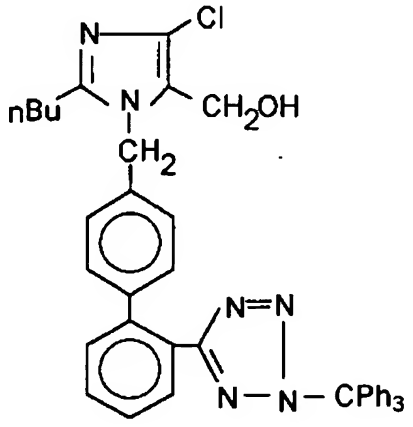


I.

This tetrazol derivative - known as losartan potassium, the chemical name of which is 2-n-butyl-4-chloro-1[(2'-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-imidazol-5-methanol potassium salt –, is the active ingredient of modern antihypertensive drugs, the angiotensin II receptor antagonists. According to WO 93/10106 and WO 95/17396 PCT Patent Applications, the losartan potassium can be synthesized from a proper acidic compound of formula (II) by reacting it with potassium hydroxide. The compound of formula (II) can be obtained from the triphenylmethyl (or trityl) protected compound of formula (III) by detritylation.

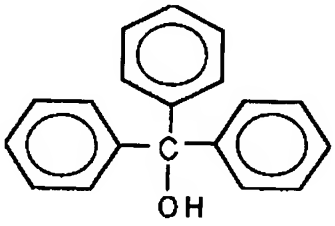


II.



III.

The cleavage of the trityl group was carried out according to the known detritylation procedures – by strong mineral acids (hydrochloric acid or sulfuric acid). The formed trityl alcohol of formula (IV) was removed from the reaction mixture either by filtration or by extraction, the recrystallized and isolated acid was transformed into losartan potassium in aqueous medium with potassium cation (potassium hydroxide or cation-exchange resin), and the latter was crystallized after treatment with organic solvent by removing the water with azeotropic distillation. The solvent of the crystallization was isopropanol or a mixture of cyclohexane and isopropanol.



IV.

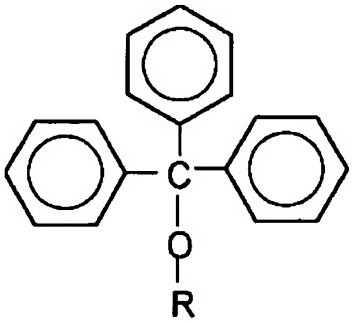
In the examples of the above patent applications the detritylation was carried out either with aqueous hydrochloric acid or with aqueous sulfuric acid in the presence of tetrahydrofuran or acetonitrile. The total yield of losartan potassium was 72 or 80 % from the acidic compound of formula (II), which was isolated after complicated operations. The disadvantages of this process are that the transformation can be carried out only in two steps, the cleavage of the trityl group proceeds by strong, corrosive mineral acid - hydrochloric acid or sulfuric acid – solution and the desired losartan potassium was isolated after addition of aqueous potassium hydroxide with complicated operations: azeotropic distillation, in low yield.

It is known, that during the synthesis of other biphenyltetrazolyl compounds, for example according to US Pat. 5,281,603, the trityl protecting group was cleaved by catalytic amount of acid in organic solvents.

According to an other known procedure, for example the one described in the US Pat. 5,281,604, the trityl group of a tetrazolyl-quinazolinone derivative is cleaved by refluxing in a mixture of methanol and tetrahydrofuran for 18 hours. The purified acidic tetrazol derivative was obtained after concentration of the reaction mixture by complicated column chromatography in low yield. From this tetrazol derivative the desired salts can be formed by known procedures.

Summing up, according to the known procedures the losartan potassium of formula (I) was prepared in all cases from the isolated and purified "losartan acid" of formula (II), which was obtained after detritylation by catalytic amount of acid.

The aim of our invention is to elaborate a process, which eliminates the disadvantages of the known, multistep procedures and according to which a high quality product can be obtained by simple technology. In our first experiments we found, that if the trityl protected 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol of formula (III) is treated with equimolar potassium hydroxide in C_1-C_4 alcohol, then the trityl-alkyl ether of formula (V) containing the alkoxy group of the alcohol and the losartan potassium of formula (I) can be obtained. If the reaction is carried out at reflux temperature for a few hours, the desired product can be obtained practically in quantitative yield.



V.

R = C_1- C_4 straight chain alkyl group

We found surprisingly that this new base catalyzed reaction proceeds very fast and the product can be obtained in high yield. During the detritylation reaction the alcohol reacted as alkoxy anion furnishing the tritylalkyl ether. The ethers of formula (V) have very low solubility in short chain alcohols and therefore can be removed by filtration.

Our other observation was that the reaction took place even if the trityl derivative of formula (III) was treated with 0.1-1 equivalent of potassium hydroxide in a short chain alcohol. In this case the detritylation proceeded in good yield – also with the formation of the trialkyl ether – and the mixture of compounds of formula (I) and (II) was formed. If the reaction mixture was treated with an alcoholic solution containing an equivalent amount of potassium hydroxide calculated on the compound of formula (II), the potassium salt of formula (I) was immediately formed.

According to the above mentioned facts the invention relates to the synthesis of losartan potassium of formula (I), chemical name: 2-n-butyl-4-chloro-1[(2'-(tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-imidazol-5-methanol potassium, starting from 2-n-butyl-4-chloro-1[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]1H-imidazol-4-methanol of formula (III), by reacting the compound of formula (III) in an alcohol of formula (VI), - wherein the meaning of R is C_1-C_4 straight chain alkyl group – with 0.1-1 equivalent of potassium hydroxide and isolating the final product of formula (I) after crystallizing out by changing the solvent to an aprotic or weakly protic solvent.

R—OH

VI.

The alcohol used in the process according to the invention is preferably methanol. The reaction is preferably carried out at 20-100 °C, more preferably at 50-80 °C.

The aprotic dipolar solvent used for the crystallization of the final product is preferably acetonitrile, or straight or branched chain or cyclic aliphatic hydrocarbons can be used as aprotic solvents as well as in an other case sec-butanol can be used as protic solvent.

The reaction can be carried out in any C_1-C_4 straight chain alcohol, but if the chain is longer the time needed for the detritylation is longer and the yield of the reaction is lower. The most preferred conditions of the reaction are guaranteed if methanol is used. In this case the yield can be even 95 % after a few hours reaction time.

If n-butanol is used in the reaction of (III) → (I) at 80 °C for 15-20 h, the yield can be higher than 80 %.

The apolar tritylalkyl ether of formula (V) formed as by-product has low solubility in the alcohol used and therefore can be removed from the reaction mixture mostly by filtration. The very pure losartan potassium can be isolated in high yield from the alcoholic filtrate by changing the solvent. After evaporating the alcohol by distillation, aprotic apolar solvents (for example cyclohexane, heptane), weakly protic secunder alcohols, such as sec-butanol and surprisingly the aprotic dipolar acetonitrile can also be used for crystallization.

The starting material 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol of formula (III) can be synthesized according to the literature: J. Med. Chem. **1991**, 34, 2525-2547 and J. Org. Chem. **1994**, 59, 6391-6394.

The advantages of the process according to our invention can be summarized as follows: the trityl alcohol of formula (IV) formed as by-product in the so far known aqueous acidic detritylation reactions is a polar compound, therefore it can be separated from the also polar losartan potassium only with substantial loss of the desired compound. The isolation of compound of formula (II) by tedious operations (extraction, filtration) was necessary in the former procedures to separate from the formed trityl alcohol. According to our process the difficult,

tedious azeotropic distillation, which was used after preparation of the potassium salt in aqueous medium, can be avoided.

Further advantage of our process is, that after the base catalyzed detritylation reaction, which proceeds in short chain alcohols – preferably in methanol – in almost quantitative yield, the about one order solubility difference in a properly chosen aprotic solvent between the formed apolar tritylalkyl ether and the polar losartan potassium makes possible the isolation of the pure, insoluble compound of formula (I) in high yield without preparing the compound of formula (II).

The invention is illustrated by the following not limiting Examples:

Example 1

Synthesis of losartan potassium of formula (I)

Under nitrogen, in a 500 ml flask a mixture of 175 ml of dry methanol, 20 g (0.026 mol) of 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol methyl-isobutyl keton solvate and 1.46 g (0.026 mol) of potassium hydroxide in 25 ml of methanol was warmed to reflux temperature over a period of 30 min. After refluxing for 4 h, the reaction was cooled to room temperature, treated with 0.6 g of charcoal and filtered. The filtrate was concentrated to a volume of 30-35 ml under diminished pressure, and after addition of 85 ml of acetonitrile again to a volume of 30-35 ml. After addition of further 85 ml of acetonitrile the solution is concentrated to a volume of 60-65 ml. The suspension was stirred at 0-(+)2 °C for 2 h, the precipitated crystals were filtered, washed three times with 30 ml of cold acetonitrile and dried at 70 °C to give 11.5 g (94 %) of the title compound.

Mp.: 262-264 °C.

Example 2

Synthesis of losartan potassium of formula (I)

Under nitrogen, in a 500 ml flask a mixture of 180 ml of dry methanol, 20 g (0.026 mol) of 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol methyl-isobutyl keton solvate and 0.1 g (0.00178 mol) of potassium hydroxide was refluxed for 3 h. The reaction mixture was cooled to room temperature and after adding 1.35 g (0.0241 mol) of potassium hydroxide in 10 ml of methanol it was treated with 0.5 g of charcoal and filtered. The filtrate was concentrated to a volume of 30 ml under diminished pressure, and after addition of 80 ml of acetonitrile again to a volume of 35 ml. After addition of further 85 ml of acetonitrile the suspension was cooled to 0 °C, the precipitated crystals were filtered after 1 h stirring, washed twice with 30 ml of cold acetonitrile and dried at 70 °C to give 11.3 g (93.4 %) of the title compound.

Mp.: 261-263 °C.

Example 3

Synthesis of losartan potassium of formula (I)

In a 500 ml flask a mixture of 200 ml of dry ethanol, 20 g (0.026 mol) of 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol methyl-isobutyl keton solvate and 1.45 g (0.026 mol) of potassium hydroxide was refluxed for 9 h, treated with 0.5 g of charcoal and filtered. The filtrate was concentrated to a volume of 30 ml under diminished pressure, and after addition of 150 ml of acetonitrile again to a volume of 60 ml. The suspension was stirred at 0 °C for 1 h, the precipitated crystals were filtered, washed twice with 25 ml of cold acetonitrile and dried at 70 °C to give 10.6 g (88 %) of the title compound.

Mp.: 262-264 °C.

Example 4

Synthesis of losartan potassium of formula (I)

In a 250 ml flask a mixture of 100 ml of n-butanol, 7.64 g (0.01 mol) of 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol methyl-isobutyl keton solvate and 0.56 g (0.01 mol) of potassium hydroxide was stirred at 80 °C for 20 h, treated with 0.5 g of charcoal and filtered. The filtrate was concentrated to a volume of 10 ml under diminished pressure, and after addition of 100 ml of acetonitrile again to a volume of 60 ml. The suspension was stirred at 0 °C for 1 h, the precipitated crystals were filtered, washed twice with 25 ml of cold acetonitrile and dried at 70 °C to give 3.78 g (82 %) of the title compound.

Mp.: 263-265 °C.

Example 5

Synthesis of losartan potassium of formula (I)

Under nitrogen, in a 500 ml flask a mixture of 200 ml of dry methanol, 20 g (0.026 mol) of 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol methyl-isobutyl keton solvate and 1.45 g (0.026 mol) of potassium hydroxide was refluxed for 3 h, treated with 0.4 g of charcoal and filtered at room temperature. The filtrate was concentrated to a volume of 30 ml under diminished pressure, and after addition of 160 ml of heptane again to a volume of 130 ml. The suspension was stirred at 0 °C for 2 h, the precipitated crystals were filtered, washed with cold heptane and dried at 70 °C to give 11.3 g (92.5 %) of the title compound.

Mp.: 263-265 °C.

Example 6

Synthesis of losartan potassium of formula (I)

The methanolic filtrate prepared according to Example 5 was concentrated to a volume of 30 ml under diminished pressure, and after addition of 150 ml of hexane again to a volume of 100 ml. The suspension was stirred at 0 °C for 1 h, the precipitated crystals were filtered, washed with cold hexane and dried to give 11.5 g (94.1 %) of the title compound.

Mp.: 262-264 °C.

What we claim is:

1.) Process for the synthesis of losartan potassium of formula (I), chemical name: 2-n-butyl-4-chloro-1-[(2'-(tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-imidazol-5-methanol potassium, starting from 2-n-butyl-4-chloro-1-[(2'-(2-triphenylmetyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazol-4-methanol of formula (III), characterized by reacting the compound of formula (III) in an alcohol of formula (VI), - wherein the meaning of R is C_1-C_4 straight chain alkyl group – with 0.1-1 equivalent of potassium hydroxide and isolating the final product of formula (I) after crystallizing out by changing the solvent to an aprotic or weakly protic solvent.

2.) The process according to claim 1, characterized by using methanol as alcohol.

3.) The process according to claim 1 and 2 characterized by, carrying out the reaction at 50-80 °C.

4.) The process according to claim 1, 2 and 3 characterized by using acetonitrile as dipolar aprotic solvent for the crystallization of the final product.

5.) The process according to claim 1, 2 and 3 characterized by using straight or branched chain or cyclic aliphatic hydrocarbons as aprotic solvent for the crystallization of the final product.

6.) The process according to claim 1, 2 and 3 characterized by using sec-butanol as protic solvent for the crystallization of the final product.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 01/00047

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/10 A61K31/41 A61P9/12 //(C07D403/10,257:00, 233:99)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 324 377 A (DU PONT) 19 July 1989 (1989-07-19) page 39 page 56 page 190 -page 191; example 316 ---	1-6
A	WO 93 10106 A (DU PONT ;MERCK & CO INC (US)) 27 May 1993 (1993-05-27) cited in the application page 19 -page 20; example 8 ---	1-6
A	WO 95 17396 A (MERCK & CO INC ;DU PONT (US); DU PONT MERCK PHARMA (US); CAMPBELL) 29 June 1995 (1995-06-29) cited in the application page 18; example 4 -----	1-6

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2001	24/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016	Seelmann, I

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INTERNATIONAL SEARCH REPORT

nformation on patent family members

International Application No
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